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Midazolam-droperidol, droperidol or olanzapine for acute agitation: A randomised clinical trial

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All authors conceived and designed the study, and contributed to the ethics committee (IRB) application. DT obtained the research funding. ST, CY and DK prepared the study packs. DT and CY supervised the study overall. JCK, JK and GP supervised the study at their respective sites. CY, JCK, JK and GP were responsible for all staff education. CY managed collation of the data and entry into the study database. CY, DT and JCK undertook the data analysis. All authors contributed to interpretation of the results, drafting and revision of the manuscript and take responsibility for the paper as a whole.

ABSTRACT

Objective

We aimed to determine the most efficacious of three common medication regimens for the sedation of acutely agitated emergency department (ED) patients.

Methods

We undertook a randomised, controlled, double-blind, triple-dummy, clinical trial in two metropolitan EDs between October 2014 and August 2015. Patients, aged 18-65 years, requiring intravenous (IV) medication sedation for acute agitation were enrolled and randomised to an IV bolus of either midazolam 5mg-droperidol 5mg, droperidol 10mg or olanzapine 10mg. Two top-up (additional) doses were administered, if required: midazolam 5mg, droperidol 5mg or olanzapine 5mg, respectively. The primary outcome was the proportion of patients adequately sedated at ten minutes.

Results

349 patients were randomized to the three groups. Baseline characteristics were similar across the groups. **Ten minutes after the first dose, significantly more patients in the midazolam-droperidol group were adequately sedated compared to the droperidol and olanzapine groups: differences in proportions (95%CI) 25.0% (12.0-38.1) and 25.4% (12.7-38.3), respectively.** ~~At any time point, patients in the droperidol and olanzapine groups were significantly less likely to be sedated compared to midazolam-droperidol patients: droperidol and olanzapine group hazard ratios (95%CI) were 0.53 (0.41-0.69) and 0.50 (0.39-0.65), respectively.~~ For times to sedation, the differences in medians (95%CI) ~~for times to sedation~~ between the midazolam-droperidol **group** and **the** droperidol ~~and midazolam-droperidol~~ and olanzapine groups were 6 (3-8) and 6 (3-7) minutes, respectively. Patients in the midazolam-droperidol group required fewer top-up doses or alternative drugs to achieve adequate sedation. The three groups' adverse event rates and lengths of stay did not differ.

Conclusion

Midazolam-droperidol combination therapy is superior, in the doses studies, to either droperidol or olanzapine monotherapy for IV sedation of the acutely agitated ED patient.

INTRODUCTION

Background

Acute agitation among emergency department (ED) patients is often associated with recreational drug and/or alcohol intoxication, mental illness or combinations of diagnoses.[1-5] The agitation may escalate to violence which is disruptive and associated with a risk of injury to the patient and those around them.[3,6] These events usually result in a 'security code' being called for an unarmed threat. De-escalation techniques are recommended initially[7] although parenteral medication sedation may be required.[3,5,6]

Importance

Sedation for acute agitation is required in 3-20 cases for every 1000 ED presentations[3,6] and the risk to the patient is real. Adverse effects are common and include airway compromise, oxygen desaturation, hypotension and extra-pyramidal events.[3,5,8-12] The challenge is to employ a medication regimen that will rapidly and effectively sedate the patient without putting them at substantial risk of adverse events. To date, a wide range of regimens have been employed, mostly including benzodiazepines and/or antipsychotic medications administered by either the intramuscular (IM) or intravenous (IV) routes. [4,8,9,13-15]

Most studies of acute agitation have been undertaken in the psychiatric setting. Hence, most evidence is not directly applicable to the ED where the onset of sedation needs to be rapid and where the pathogenesis of the agitation is often undifferentiated.[5] Currently, ED sedation guidelines are often inconsistent, poorly supported by evidence and frequently not followed.[13] Furthermore, sedation practice is evolving with new medications being incorporated into practice in unapproved settings or routes of administration e.g. IV olanzapine.[16]

Goals of this Investigation

Recent research suggests that medication combination regimens are superior to monotherapy.[1,13,15] Chan et al.[1] reported that both IV midazolam-droperidol and IV midazolam-olanzapine combinations are superior to IV midazolam monotherapy. The relevance of this finding is that benzodiazepine monotherapy, especially midazolam, is currently the most commonly used regimen for acute agitation management in some parts of the world.[13,15] Droperidol[4,13,15] and, more recently, olanzapine[4,12,16,17] are also used as monotherapy. To date, the efficacy of the midazolam-droperidol combination in acute agitation has not been compared with either droperidol or olanzapine monotherapy. We compared these three regimens and hypothesised that the midazolam-droperidol combination would be the superior regimen.

METHODS

Study Design and Setting

We undertook a randomised, controlled, double-blind, triple-dummy, clinical trial in the EDs of two inner city, tertiary referral, Australian hospitals with annual censuses of 45,000 and 70,000 adult patients. Each ED is supported by 24 hour co-located psychiatric services. Patients were enrolled between October 2014 and August 2015, inclusive. The trial was registered on the Australian and New Zealand Clinical Trials Registry, (ACTRN ACTRN12607000591459) and approved by the Human Research Ethics Committees (HREC) of the participating institutions.

Selection of Participants

Patients were eligible for inclusion if they were aged 18-65 years (inclusive) and required IV medication sedation for acute agitation, as determined by their attending ED doctor. Patients were excluded if they had been previously enrolled, had a known hypersensitivity or contraindication to a study medication, a reversible aetiology for their agitation (hypotension, hypoxia, hypoglycaemia), were experiencing acute alcohol withdrawal or were pregnant.

Enrolment was based upon patient and staff safety considerations and not sedation scores. Patients who received a sedative medication(s) within the previous 12 hours, either as usual medications or pre-hospital treatment, were eligible if they met other eligibility criteria. Due to the level of agitation, informed patient consent was not possible and HREC approval was given for waiver of consent.

Methods and Measurements

Patients were assigned to a midazolam-droperidol combination arm, a droperidol monotherapy (droperidol) arm or an olanzapine monotherapy (olanzapine) arm (Figure 1). The first and top-up (additional) doses, respectively, were midazolam 5mg plus droperidol 5mg and midazolam 5mg; droperidol 10mg and 5mg; olanzapine 10mg and 5mg (see Web Appendix). Doses were determined from clinical practice[13,16,17] and previous trials[1,5] and were administered by rapid IV push. The midazolam-droperidol combination was chosen over midazolam-olanzapine as droperidol is more commonly used.[13,18]

Study packs were pre-assembled by the Pharmacy Department of a third hospital. Each contained a patient identification code, instructions, a case report form, vials of repackaged medication/placebo, water for reconstitution, normal saline for dilution, disposables, and a sealed envelope with a description of the vial contents (if un-blinding were required).

At each site, study packs were 'block randomised' in groups of six (two for each study arm) to ensure approximately equal numbers of patients in each arm. A pharmacist not involved with patient enrolment, data collection or analysis, conducted the randomisation using random-number tables and kept the codes confidential.

Midazolam and droperidol are clear liquids. Olanzapine is a yellow powder that requires reconstitution to a yellow liquid. To achieve blinding, a 'triple-dummy' technique was employed. Normal saline was used for the clear liquid placebos. Soluvit N®, a vitamin and mineral preparation designed for IV parenteral nutrition, was used as the olanzapine placebo. Soluvit N® has been successfully employed as an olanzapine placebo.[1]

Consecutive patient enrolment was undertaken by assigning patients to the next sequential study pack at their site. Details of the vial contents and preparation, the administered volumes and doses are described in Web Appendix.

If adequate sedation was not achieved within 5 minutes of the first dose, a top-up dose was administered. A second top-up dose was administered 5 minutes later, if required. If adequate sedation was not achieved 5 minutes after the second top-up dose, the ED doctor could administer additional, open label, sedative medication(s) at his/her discretion. At this stage, the doctor could un-blind the study medication(s) if this was deemed necessary for patient safety.

Senior ED nurses recorded the level of patient sedation, and all adverse events and their management. Patient sedation was measured using a 6-point, validated sedation scale[19] (5–highly aroused, violent; 4–highly aroused, possibly distressed or fearful; 3–moderately aroused, unreasonable or hostile; 2–mildly aroused, willing to talk reasonably; 1–minimal agitation; 0–asleep). Scores were recorded at baseline (immediately prior to first dose administration) and every five minutes until 60 minutes after sedation was achieved. Adequate sedation was defined as a score ≤ 2 or when no further sedation was required, as determined by the treating doctor. All patients received standard sedation care including 1:1 nursing and regular monitoring of sedation level, vital signs, cardiac rhythm and adverse events.

Outcomes

The primary outcome was the proportion of patients adequately sedated within 10 minutes of the first dose administration.

The secondary outcomes included **time to adequate sedation,** the need for re-sedation <60 minutes after achieving sedation, re-sedation from 60 minutes after sedation until ED discharge, sedation medication 'failure' (alternate medications required), electrocardiogram QTc interval and adverse events.

Analysis

Chan et al.[1] reported that the proportion of patients adequately sedated at 10 minutes in their midazolam-droperidol arm was 66.1%. We determined that a proportion less than two-thirds of this proportion (i.e. 44%) would represent a clinically significant difference between the midazolam-droperidol and either of the other arms. To demonstrate this difference in the proportions (66% versus 44%), at least 114 patients were required in each arm (2-sided, power 0.9, level of significance 0.05). Hence, a sample size of at least 342 patients was required.

Data analysis employed the 'Intention to Treat' principle. Most data are presented descriptively, including graphically. **The proportions of patients adequately sedated at 10 minutes were analysed using differences in proportions (95% confidence intervals [95% CI]).** Time to sedation was analysed using difference in medians (95% CI) and survival-time data, and was plotted using a Kaplan-Meier curve. Hazard ratios (HR, 95% CI) for adequate sedation were generated using the midazolam-droperidol group as a baseline reference and Multivariable Cox's Regression was used to adjust for regular medications and medications

administered prior to the study medication. IBM SPSS Statistics for Windows (version 23, Armonk. NY: IBM Corp.) was used for all analyses. Un-blinding was undertaken only after all analyses were complete.

RESULTS

Characteristics of Study Subjects

Of 424 patients screened, 361 were enrolled (see Figure 1). An additional 12 patients were excluded for either missing primary endpoint data or repeat enrolment. Data from the remaining 349 patients (96.7% of those eligible) were analysed. The patient baseline characteristics are reported in Table 1. ~~There were no significant differences between the groups.~~ **For these characteristics, the gross magnitude of the differences between the groups does not appear large enough to confound the analysis.**

Main Results

Ten minutes after the first sedative dose, significantly more patients in the midazolam-droperidol group were adequately sedated compared to the droperidol and olanzapine groups: differences in proportions (95%CI) 25.0% (12.0-38.1) and 25.4% (12.7-38.3), respectively. At each time point after the first dose, significantly fewer patients were adequately sedated in the droperidol and olanzapine groups: hazard ratios (95%CIs): 0.53 (0.41-0.69) and 0.50 (0.39-0.65), respectively (Table 2, Figure 2). The Multivariable Cox Regression indicated that other medications had negligible impact on the hazard ratios.

The median time to adequate sedation for the midazolam-droperidol group was significantly shorter than both the droperidol and olanzapine groups (Table 2). The difference in medians (95%CI) for times to sedation between the midazolam-droperidol and droperidol, and midazolam-droperidol and olanzapine groups were 6 (3-8) and 6 (3-7) minutes, respectively.

Fewer patients in the midazolam-droperidol group required top-up doses or medications other than top-up doses (Table 3). The groups did not differ in the proportion of patients who required re-sedation after initial adequate sedation had been achieved.

The proportion of patients in each group who experienced an adverse event did not differ (Table 4). Most events were related to respiratory depression and were readily managed with no patient requiring endotracheal intubation.

An electrocardiogram was obtained within 30 minutes of the first dose in 193 (55.3%) patients: midazolam-droperidol 71 (60.2%), droperidol 61 (55.0%) and olanzapine 61 (50.8%). The median (range) QT_c intervals (msec) of the three groups were similar: 450 (325-501), 442 (320-501) and 445 (313-501), respectively. No patient experienced a cardiac adverse event.

There were a total of four protocol violations (Figure 1). All occurred because the patients' ages were not known at the time that sedation was deemed necessary. The study age criteria were established for safety reasons only. The four patients were included in the data analysis because of our intention to treat analysis. Re-analysis of the data after their exclusion did not change the results.

The median (IQR) ED lengths of stay (hours) for the midazolam-droperidol, droperidol and olanzapine groups were similar: 11.0 (7.0-14.6), 9.1 (6.2-13.3) and 10.7 (7.3-14.8), respectively. The groups did not differ in places of patient disposition following ED discharge. In each group, slightly more than one half of patients were discharged to home and approximately one quarter were admitted to a psychiatric ward. The remaining patients were

discharged to observation or medical wards, police or correctional facilities or assisted accommodation. Six patients absconded.

LIMITATIONS

A slightly greater proportion of the midazolam-droperidol group had less urgent triage categories, a history of mental illness and a disposition to a psychiatry ward. However, these differences were minor and unlikely to have introduced confounding. **Additionally, our analysis did not account for multiple comparisons.**

The sedation scale was potentially subject to measurement bias. However, the scale has been validated, the ED staff were fully trained in its use and it has proven reliable in our earlier trials.[1,5] Also, any bias was likely to have been evenly distributed across all groups and minimised by blinding of the ED staff.

Almost one half of all patients did not have an electrocardiogram recorded and this may have introduced selection bias. Although unlikely, it is possible that some patients with substantial QTc abnormalities were not identified.

In this study, the first and top-up doses for each group were equivalent (total 10mg and 5mg, respectively). However, it was not simply assumed that the potencies at these doses would be equivalent. All doses were determined by careful examination of the doses commonly used in clinical practice[13] and our earlier trials[1,5].

The internal validity of this study should be maximised by the use of very similar peer-reviewed methodology.[1,5] As patients were enrolled at only two centres, the external validity may be questionable. However, our patients are likely to be similar to those from other centres.

DISCUSSION

This study demonstrates that, in the doses studied, a midazolam-droperidol combination is significantly more efficacious than droperidol or olazapine monotherapy in achieving rapid and adequate sedation. This is evidenced by higher proportions of patients sedated at any time point, shorter times to sedation, and lower proportions requiring additional sedatives with the combination regimen.

The adverse event profiles of the three regimens did not differ although respiratory events were slightly more common in the midazolam-droperidol group. This is consistent with reports of respiratory compromise associated with midazolam sedation for both acute agitation[1,5] and painful procedures[20]. Importantly, the incidence of acute dystonia was low.

As the midazolam-droperidol combination in this study was identical to the midazolam-droperidol combination of Chan et al[1], the two can be compared directly. The median times to sedation for the two midazolam-droperidol groups were five and six minutes, respectively. This similarity provides strong and consistent evidence of the efficacy of this midazolam-droperidol combination. Although the proportions of patients adequately sedated at 5 minutes differed (55.9% versus 35.7%, respectively), this was likely due to differences in patient characteristics. In particular, there were more intoxicated (drugs and/or alcohol) patients in the current study (48.3% versus 30.4%, respectively).

The midazolam-droperidol combination has been examined previously. Chan et al.[1] reported that the midazolam-olanzapine combination has very similar effectiveness and safety profiles. Although the midazolam-olanzapine combination has not been directly compared with

droperidol or olanzapine monotherapy, it is likely that this combination may serve as an effective alternative in jurisdictions where droperidol is not used.

Traditionally monotherapy, administered either IV or IM, has been employed for the sedation of acutely agitated ED patients.[4,9,13] Trials have examined benzodiazepines (midazolam, diazepam, lorazepam, clonazepam) [1,5,8,11,21-23], conventional antipsychotics (chlorpromazine, haloperidol, droperidol) [5,8,10,11,13,21-26] and atypical antipsychotics (olanzapine, ziprasidone). [13,21,27-29] There is now increasing interest in medication combinations. The effectiveness of several combinations have been examined including benzodiazepine-droperidol[1], benzodiazepine-olanzapine[1,30], benzodiazepine-haloperidol[8,30] and haloperidol-promethazine[11,24,28,31].

While monotherapy may be simpler to administer, its mechanisms are largely limited to single biochemical pathways. Unfortunately, trials of medication combinations have suffered from uncontrolled medication re-dosing, lack of blinding and settings other than the ED.[8,11,24,28,31] There is, however, some evidence that combinations produce more rapid sedation[1,13,15], less need for re-sedation[1] , reduced benzodiazepine dosage[1] and have comparable adverse event profiles[1]. As most studies of combination therapy have used the IM route, comparisons with this study are difficult. To our knowledge, this is only the second study to have examined IV medication combinations.[1]

Sedation with droperidol is becoming increasingly common.[4,6,13] However, its widespread use is hindered by a 'black box' warning related to QTc interval prolongation.[32] There is now increasing evidence that droperidol has a good safety profile in the ED setting.[1,3,5,14,23,25] In a

Position Statement, Perkins et al.[33] described droperidol as effective and safe. The findings of our trial provide additional evidence for the safety of droperidol.

Olanzapine has a relatively benign side effect profile. However, a Cochrane review[27] of IM olanzapine for acutely agitated patients concluded that published studies had poorly reported outcomes and the potential for bias. No trials in the ED setting were included. Subsequently, one ED study supported the safety of olanzapine administered by the IM route.[30] Olanzapine is increasing being used intravenously (off label)[13,16,17] and one retrospective study supports the safety of IV olanzapine in the ED setting.[29] To date, only one clinical trial has examined its effects via the IV route.[1] In that study, it appeared safe at the 5 mg dose and in combination with midazolam.[1] The present study provides additional evidence that IV olanzapine is safe.

Both IV and IM routes are commonly used for sedative medication administration. The IV and IM routes are preferred in Australasia[13] and Hong Kong [15], respectively. The IV route is often recommended[7,19,34,35] as the IM route may be unpredictable, have a slower onset and cannot be used for accurate titration. However, IV administration requires cannulation of the patient. This usually requires physical restraint which may not be an option in EDs with limited security or ED staff resources. To date, no published clinical trials have compared the effectiveness of sedatives administered by these two routes.

In summary, this study demonstrates that, in the doses studied, the IV midazolam-droperidol combination provides significantly more rapid and effective sedation than the IV droperidol or olanzapine monotherapy regimens. Also, it required fewer top-up doses or other medications to achieve adequate sedation. It is recommended that the midazolam-droperidol

combination should be used for the sedation of acutely agitated ED patients regardless of whether or not the cause of the agitation is known.

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Neither organization had any role in the design or execution of the study, data analysis or interpretation.

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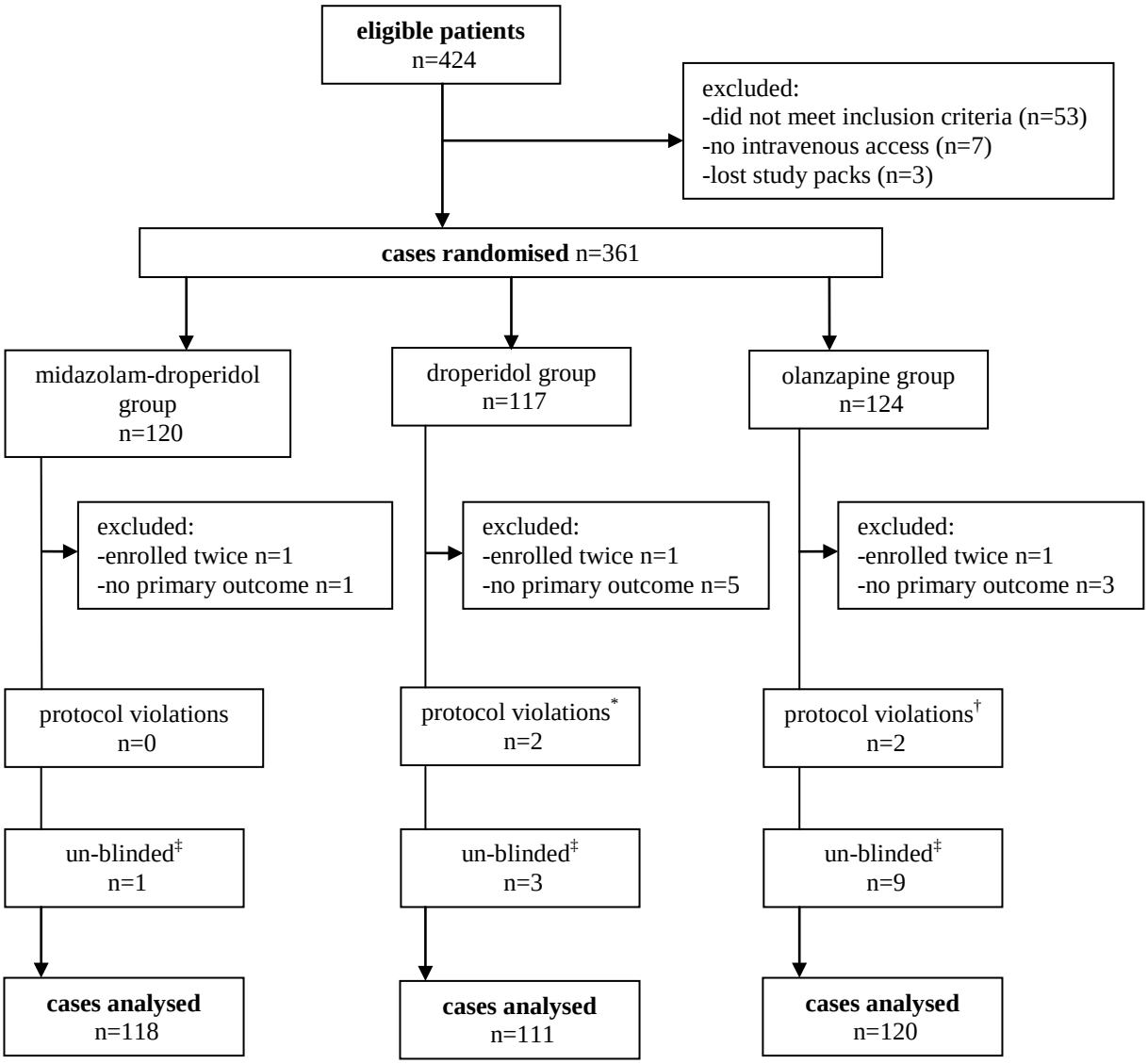
Figure 1. Patient flow through the study (modified CONSORT diagram)



*patients aged 15 and 71 years

†patients aged 68 and 69 years

‡patient sedation difficult and un-blinding undertaken to inform clinical decision making. No un-blinding was undertaken in response to adverse events.

Figure 2. Kaplan-Meier curve comparing the proportion of patients sedated as a function of time.

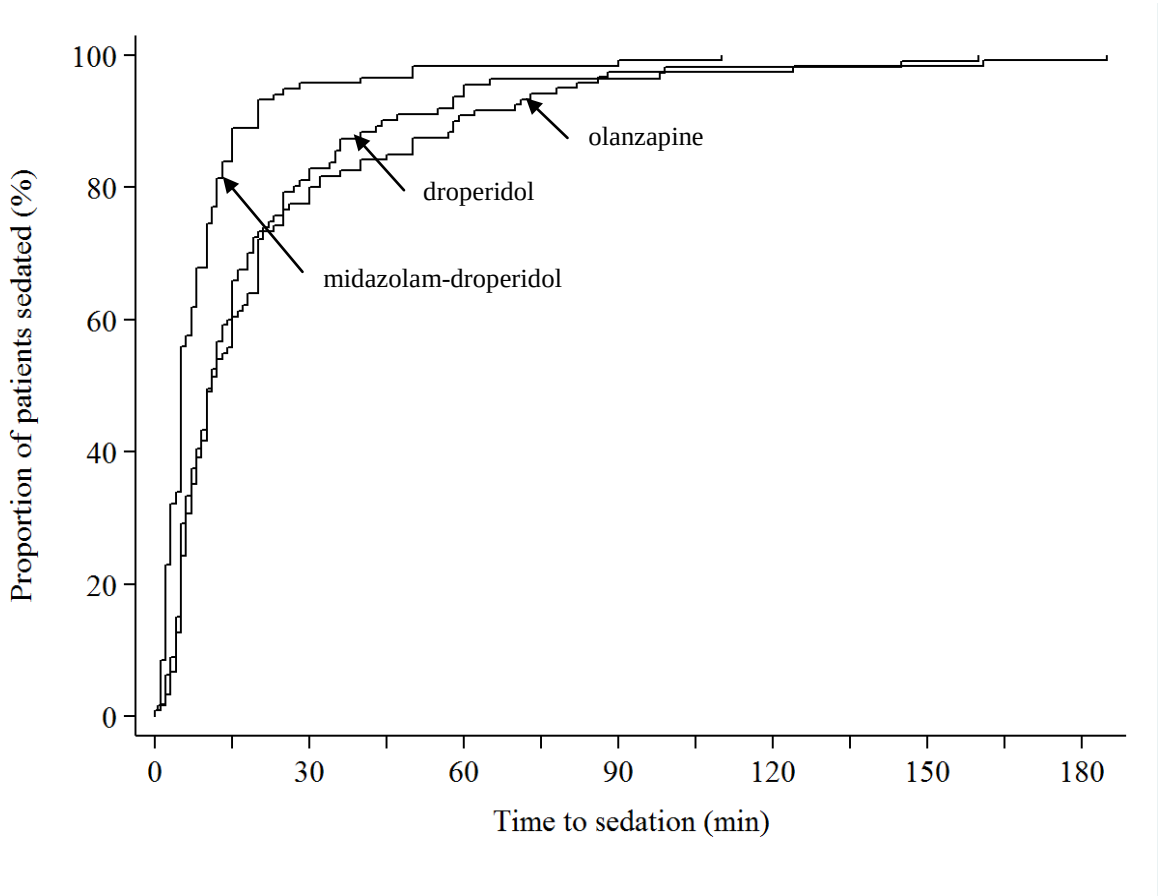


Table 1. **Baseline patient characteristics***

	midazolam-droperidol n=118	droperidol n=111	olanzapine n=120
Age, years, mean (95%CI)	34 (32-36)	34 (32-36)	35 (33-37)
Male, n (%)	72 (61.0)	68 (61.3)	69 (57.5)
ATS category, n (%)			
1. Resuscitation	5 (4.2)	6 (5.4)	9 (7.5)
2. Emergency	40 (33.9)	50 (45.0)	50 (41.7)
3. Urgent	69 (58.5)	49 (44.1)	56 (46.7)
4. Semi-urgent	4 (3.4)	6 (5.4)	5 (4.2)
5. Non-urgent	0 (0.0)	0 (0.0)	0 (0.0)
Waiting time from triage to be seen by a doctor, minutes, median (IQR)	23 (4-53)	12 (4-31)	21 (3-44)
ICD-10 category, n (%)			
Intoxication (drugs and/or alcohol)	57 (48.3)	61 (55.0)	65 (54.2)
Mental illness[†]	56 (47.5)	45 (40.5)	47 (39.2)
Organic illness[‡]	5 (4.2)	5 (4.5)	8 (6.6)
Substance abuse history[§], n (%)	95 (80.5)	103 (92.8)	100 (83.3)
Usual psychotropic medications, n (%)	33 (28.0)	29 (26.1)	34 (28.3)
Benzodiazepines	8 (6.8)	4 (3.6)	6 (5.0)
SSRI or SNRI	6 (5.1)	7 (6.3)	7 (5.8)
Atypical antipsychotics	10 (8.5)	14 (12.6)	18 (15.0)
Depot antipsychotics	2 (1.7)	4 (3.6)	3 (2.5)
Conventional antipsychotics	5 (4.2)	3 (2.7)	3 (2.5)

Need for physical restraint, n (%)	85 (72.0)	86 (77.5)	93 (77.5)
Sedatives prior to enrolment[¶], n (%)	32 (27.1)	30 (27.0)	26 (21.7)
Police attendance on arrival, n (%)	80 (67.8)	78 (70.3)	93 (77.5)
Mode of arrival, n (%)			
Road ambulance	69 (58.5)	67 (60.4)	69 (57.5)
Police	41 (34.8)	37 (33.3)	42 (35.0)
Other[¥]	8 (6.7)	7 (6.3)	9 (7.5)

ATS, Australasian Triage Scale; IQR, Interquartile Range; ICD-10, International Classification of Diseases, 10th Revision; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin noradrenaline reuptake inhibitor.

[†]Mental illness includes psychoses, anxiety, depressive illnesses and trauma as a consequence of suicide attempt; [‡]Organic illness includes infections, delirium due to an organic cause and all other trauma; [§]Substances include drugs and/or alcohol; [¶]Sedatives (i.e. benzodiazepines and antipsychotics) prior to study enrolment include those administered in the pre-hospital care setting (i.e. administered by paramedics) or when in the ED; [¥]Other modes of transport include private travel (i.e. self, family, friends).

Table 2. ~~Primary Endpoints:~~ Proportions of patients sedated at specific time points after first dose administration and median times to adequate sedation

	midazolam-droperidol n=118	droperidol n=111	olanzapine n=120
Proportion sedated, n (%)			
at 5 minutes	66 (55.9)	27 (24.3)	35 (29.2)
at 10 minutes	88 (74.6)	55 (49.6)	59 (49.2)
at 15 minutes	105 (89.0)	67 (60.4)	79 (65.8)
at 30 minutes	113 (95.8)	92 (82.9)	96 (80.0)
at 60 minutes	116 (98.3)	106 (95.5)	109 (90.8)
Time to sedation, mins, median (IQR)	5 (3-11)	11 (6-23)	11 (5-25)

IQR inter-quartile range

Table 3. Secondary endpoints, the need for addition parenteral sedative medication (patients may be administered more than one medication)

	midazolam -droperidol n=118	droperidol n=111	olanzapine n=120
Number of top-up doses required to reach initial adequate sedation, n (%)			
0	85 (72.0)	45 (40.5)	47 (39.2)
1	25 (21.2)	30 (27.0)	29 (24.2)
2	8 (6.8)	36 (32.4)	44 (36.7)
Need for additional parenteral medications to reach initial adequate sedation*, n (%)	2 (1.7)	15 (13.5)	31 (25.8)
midazolam	2 (1.7)	12 (10.8)	27 (22.5)
droperidol	0 (0.0)	5 (4.5)	9 (7.5)
olanzapine	2 (1.7)	1 (0.9)	8 (6.7)
ketamine	0 (0.0)	1 (0.9)	0 (0.0)
Need for additional parenteral re-sedation <60 minutes after initial adequate sedation, n (%)	7 (5.9)	5 (4.5)	10 (8.3)
midazolam	5 (4.2)	3 (2.7)	8 (6.7)
droperidol	3 (2.5)	2 (1.8)	3 (2.5)
olanzapine	3 (2.5)	1 (0.9)	4 (3.3)
ketamine	0 (0.0)	1 (0.9)	0 (0.0)

Need for additional parenteral re-sedation from 60 minutes after initial adequate sedation, until ED discharge, n (%)	26 (22.0)	16 (14.4)	28 (23.3)
midazolam	18 (15.3)	12 (10.8)	23 (19.2)
droperidol	14 (11.9)	4 (3.6)	9 (7.5)
olanzapine	8 (6.8)	4 (3.6)	9 (7.5)
ketamine	0 (0.0)	1 (0.9)	1 (0.8)

*additional parenteral sedatives include medication doses required in addition to the study medication top-up doses.

Table 4. Reported adverse events

	midazolam-droperidol n=118	droperidol n=111	olanzapine n=120
Number of patients with reported events, n (%)[*]	26 (22.0)	18 (16.2)	24 (20.0)
airway obstruction[†]	11 (9.3)	4 (3.6)	5 (4.2)
oxygen desaturation[†] (SaO_2 <90%)	17 (14.4)	7 (6.3)	13 (10.8)
hypotension[‡] (SBP <80 mmHg)	2 (1.7)	4 (3.6)	1 (0.8)
bradycardia (HR <60 beats/min)	0 (0.0)	2 (1.8)	5 (4.2)
prolonged QTc[§] (QTc interval >500ms)	1 (0.8)	3 (2.7)	3 (2.5)
acute dystonia[¶]	1 (0.8)	0 (0.0)	2 (1.7)
hypoventilation (RR <10 breaths/min)	0 (0.0)	1 (0.9)	1 (0.8)

SaO2 arterial oxygen saturation, SBP systolic blood pressure, HR heart rate, RR respiratory rate

[*]Patients may have experienced more than one event; [†]All cases of airway obstruction and oxygen desaturation were transient and resolved with jaw thrust, lateral positioning, with or without supplemental oxygen; [‡]All cases resolved after the administration of fluids, without sequelae; [§]No clinical symptoms and no treatment was required for all cases of prolonged QTc; [¶]All cases resolved without sequelae, one case in the olanzapine group required benztropine

Web Appendix - Medication Vial Preparation and Dosage Regimen

Medication vial preparation:

After enrolment, the two clear liquid vials (A and B) were drawn up and the yellow powder vial (C) was reconstituted and drawn up. The first dose of sedative(s) comprised contents from all three vials (two clear and one yellow liquid). Top-up doses, if required, comprised contents from two vials only (one clear and one yellow liquid).

Medication regimen:

1. Midazolam-droperidol combination (control) arm:

	Vial A	**Vial B**	**Vial C**
	midazolam (15mg/15ml) (clear solution)	droperidol (5mg/2ml) (clear solution)	placebo 2 x (10ml) (yellow solution)
First dose	5mg (5ml)	5mg (2ml)	0mg (10ml)
1st top-up dose (if required)	5mg (5ml)	no dose	0mg (5ml)
2nd top-up dose (if required)	5mg (5ml)	no dose	0mg (5ml)

NB. minimum (maximum) total dose: midazolam 5mg (15mg), droperidol 5mg (5mg)

2. Droperidol monotherapy (droperidol) arm:

	Vial A	**Vial B**	**Vial C**
	droperidol (15mg/15ml) (clear solution)	droperidol (5mg/2ml) (clear solution)	placebo 2 x (10ml) (yellow solution)
First dose	5mg (5ml)	5mg (2ml)	0mg (10ml)
1st top-up dose (if required)	5mg (5ml)	no dose	0mg (5ml)
2nd top-up dose (if required)	5mg (5ml)	no dose	0mg (5ml)

NB. minimum (maximum) total dose: droperidol 10mg (20mg)

3. Olanzapine monotherapy (olanzapine) arm:

	Vial A	**Vial B**	**Vial C**
	placebo (15ml) (clear solution)	placebo (2ml) (clear solution)	olanzapine 2 x (10mg/10ml) (yellow solution)
First-dose	0mg (5ml)	0mg (2ml)	10mg (10 ml)
1st top-up dose (if required)	0mg (5ml)	no dose	5mg (5ml)
2nd top-up dose (if required)	0mg (5ml)	no dose	5mg (5ml)

NB. minimum (maximum) dose: olanzapine 10mg (20mg)